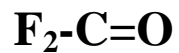


**ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)  
FOR  
CARBONYL FLUORIDE  
(CAS Reg. No. 353-50-4)**



**INTERIM**

**ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)  
FOR  
CARBONYL FLUORIDE  
(CAS Reg. No. 353-50-4)**

**INTERIM**

## PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m<sup>3</sup>]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL

## TABLE OF CONTENTS

1			
2	PREFACE .....		3
3	LIST OF TABLES .....		6
4	EXECUTIVE SUMMARY .....		7
5	1. INTRODUCTION .....		8
6	2. HUMAN TOXICITY DATA .....		9
7	2.1. Acute Lethality .....		9
8	2.1.1. Case Reports .....		9
9	2.2. Nonlethal Toxicity .....		9
10	2.2.1. Odor Threshold/Odor Awareness .....		9
11	2.2.2. Case Reports .....		9
12	2.2.3. Epidemiologic Studies .....		9
13	2.3. Developmental/Reproductive Toxicity .....		9
14	2.4. Genotoxicity .....		9
15	2.5. Carcinogenicity .....		10
16	2.6. Summary .....		10
17	3. ANIMAL TOXICITY DATA .....		10
18	3.1. Acute Lethality .....		10
19	3.1.1. Rats .....		10
20	3.2. Nonlethal Toxicity .....		11
21	3.2.1. Rats .....		11
22	3.3. Repeated Dose Toxicity .....		12
23	3.4. Developmental/Reproductive Toxicity .....		12
24	3.5. Genotoxicity .....		12
25	3.6. Chronic Toxicity/Carcinogenicity .....		12
26	3.7. Summary .....		12
27	4. SPECIAL CONSIDERATIONS .....		13
28	4.1. Metabolism and Disposition .....		13
29	4.2. Mechanism of Toxicity .....		13
30	4.3. Structure Activity Relationships .....		13
31	4.4. Other Relevant Information .....		13
32	4.4.1. Species Variability .....		14
33	4.4.2. Susceptible Populations .....		14
34	4.4.3. Concentration-Exposure Duration Relationship .....		14
35	4.4.4. Concurrent Exposure Issues .....		14
36	5. DATA ANALYSIS FOR AEGL-1 .....		14
37	5.1. Summary of Human Data Relevant to AEGL-1 .....		14
38	5.2. Summary of Animal Data Relevant to AEGL-1 .....		14
39	5.3. Derivation of AEGL-1- Values .....		14
40	6. DATA ANALYSIS FOR AEGL-2 .....		15
41	6.1. Summary of Human Data Relevant to AEGL-2 .....		15
42	6.2. Summary of Animal Data Relevant to AEGL-2 .....		15
43	6.3. Derivation of AEGL-2 Values .....		15
44	7. DATA ANALYSIS FOR AEGL-3 .....		15
45	7.1. Summary of Human Data Relevant to AEGL-3 .....		15
46	7.2. Summary of Animal Data Relevant to AEGL-3 .....		15
47	7.3. Derivation of AEGL-3 Values .....		15
48	8. SUMMARY OF AEGLS .....		16
49	8.1. AEGL Values and Toxicity Endpoints .....		16
50	8.2. Comparison with Other Standards and Guidelines .....		16
51	8.3. Data Adequacy and Research Needs .....		17

1	9. REFERENCES .....	19
2	APPENDIX A: DERIVATION OF AEGL VALUES.....	21
3	APPENDIX B: TIME-SCALING CALCULATIONS .....	26
4	APPENDIX C: DERIVATION SUMMARY FOR CARBONYL FLUORIDE AEGLS.....	28
5	APPENDIX D: BENCHMARK DOSE CALCULATIONS .....	31
6	APPENDIX E: CATEGORY PLOT FOR CARBONYL FLUORIDE .....	36
7		

## LIST OF TABLES

TABLE 1. Summary of AEGL Values for Carbonyl Fluoride .....	8
TABLE 2. Chemical and Physical Properties of Carbonyl Fluoride .....	9
TABLE 3. Summary of Acute Inhalation Data in Laboratory Animals .....	11
TABLE 4. Repeated Dose Inhalation Data in Laboratory Animals.....	12
TABLE 5. AEGL-1 Values for Carbonyl Fluoride.....	14
TABLE 6. AEGL-2 Values for Carbonyl Fluoride.....	15
TABLE 7. AEGL-3 Values for Carbonyl Fluoride.....	16
TABLE 8. Summary of AEGL Values for Carbonyl Fluoride .....	16
TABLE 9. Extant Standards and Guidelines for Carbonyl Fluoride.....	17

## EXECUTIVE SUMMARY

Carbonyl fluoride is a colorless, irritating gas, with a pungent odor. It is very hygroscopic, and is hydrolyzed into carbon dioxide and hydrogen fluoride by water. It is used as an intermediate in the synthesis of organic compounds. The thermal decomposition of fluoropolymers such as polytetrafluoroethylene and polyfluoroethylenepropylene is a major source of exposure as the major reaction product from the rapid destruction of plastic materials at temperatures above 500 °C is carbonyl fluoride. Carbonyl fluoride is a strong irritant to the eyes and respiratory tract. The irritancy of carbonyl fluoride is hypothesized to be due to hydrogen fluoride, a known sensory irritant. However, the toxicity of carbonyl fluoride is greater than that attributed to hydrogen fluoride, and may be the result of deep penetration into the lungs as well as the production of hydrogen fluoride.

Exposure-response data from rat studies were used to derive acute exposure guideline level (AEGL) values for carbonyl fluoride due to lack of quantitative data from human case reports. The AEGL values for the exposure periods of concern were scaled from the experimental exposure duration using exponential scaling ( $C^n \times t = k$ , where  $C$  = exposure concentration,  $t$  = exposure duration, and  $k$  = a constant). Data are unavailable to empirically derive a scaling factor ( $n$ ) for carbonyl fluoride. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by  $C^n \times t = k$ , where the exponent  $n$  ranges from 0.8 to 3.5 (ten Berge et al. 1986). Temporal scaling was performed using  $n = 3$ , when extrapolating to shorter time points and  $n = 1$  when extrapolating to longer time points for AEGL values (NRC 2001). The 30-minute AEGL value was adopted for the 10-minute value according to the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001).

No data on exposure of humans were located.

No AEGL-1 values were derived due to insufficient data.

In the absence of empirical data, the AEGL-2 values were derived by dividing the AEGL-3 values by 3 according to AEGL guidelines (NRC 2001). Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep concentration-response curve (DuPont, 1976).

The AEGL-3 values were derived by applying the BMCL<sub>05</sub> of 5.2 ppm from a rat study by DuPont (1976). Rapid to convulsive respiration and pulmonary edema were observed in rats exposed for 4 hours. Death occurred at all concentrations. An interspecies uncertainty factor of 3 was applied because it is not expected that the toxicity of the direct acting irritant would differ among species. Some support is provided by Scheel et al. (1968a) who generated carbonyl fluoride via polytetrafluoroethylene pyrolysis. Exposure to 310 ppm in rats resulted in focal hemorrhage of the lung and pulmonary edema, observed at 24 hours postexposure. The authors stated that this effect was produced at the same concentration in other species including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lung were not provided for these species. Carbonyl fluoride also has a steep concentration-response curve. Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced

dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976). An intraspecies uncertainty factor of 3 was applied because carbonyl fluoride is a direct acting irritant of the lung and the respiratory effects due to irritation are not expected to differ greatly among individuals. Carbonyl fluoride also has a steep-concentration response which may be an indication of a small variation of toxic effects within a population.

The calculated values are listed in the table below.

**TABLE 1. Summary of AEGL Values for Carbonyl Fluoride**

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 <sup>a</sup> (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	0.35 ppm (0.95 mg/m <sup>3</sup> )	0.35 ppm (0.95 mg/m <sup>3</sup> )	0.28 ppm (0.76 mg/m <sup>3</sup> )	0.17 ppm (0.46 mg/m <sup>3</sup> )	0.087 ppm (0.23 mg/m <sup>3</sup> )	One-third of the AEGL-3 values (NRC 2001)
AEGL-3 (Lethal)	1.0 ppm (2.7 mg/m <sup>3</sup> )	1.0 ppm (2.7 mg/m <sup>3</sup> )	0.83 ppm (2.2 mg/m <sup>3</sup> )	0.52 ppm (1.4 mg/m <sup>3</sup> )	0.26 ppm (0.70 mg/m <sup>3</sup> )	4-hr rat BMCL <sub>05</sub> (DuPont 1976)

<sup>a</sup> Carbonyl fluoride is a sensory irritant; the odor has been described as pungent and irritating.

NR:= Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL concentration is without adverse effects.

## 1. INTRODUCTION

Carbonyl fluoride is a colorless, pungent and irritating gas. It is very hygroscopic, and is hydrolyzed by water (O'Neil et al. 2001). Chemical and physical properties are listed in Table 2. Carbonyl fluoride can be prepared from fluorine or bromine trifluoride and carbon monoxide. Alternately, it can be prepared by the action of silver fluoride on carbon monoxide or through the reaction of phosgene with sodium fluoride and hydrogen cyanide. It is a thermal decomposition product of fluoropolymers such as polytetrafluoroethylene and polyfluoroethylenepropylene heated to temperatures above 500 °C. Carbonyl fluoride is used as a chemical intermediate in the synthesis of organic compounds such as fluorinated alkyl isocyanates (O'Neil et al. 2001; HSDB 2006). Recent production data were not located. Carbonyl fluoride is shipped as a liquefied compressed gas (NIOSH 2006).

TABLE 2. Chemical and Physical Properties of Carbonyl Fluoride

Parameter	Value	References
Synonyms	Carbon difluoride oxide; carbon fluoride oxide; carbon oxyfluoride; carbonyl difluoride; fluoroformyl fluoride; fluorophosgene	NIOSH 2006
Chemical formula	COF <sub>2</sub>	O'Neil et al. 2001
Molecular weight	66.01	O'Neil et al. 2001
CAS Reg. No.	353-50-4	O'Neil et al. 2001
Physical state	Colorless gas	O'Neil et al. 2001
Solubility in water	Unstable in presence of water, very hygroscopic	O'Neil et al. 2001; ACGIH 2006
Vapor pressure	4.45 x 10 <sup>4</sup> mm Hg at 25 °C	HSDB 2006
Vapor density (air =1)	2.29	ACGIH 2006
Liquid density (water =1)	Not applicable	
Melting point	-114 °C	HSDB 2006
Boiling point	-83 °C	HSDB 2006
Flammability limits	Nonflammable	NIOSH 2006
Conversion factors	1 ppm = 2.7 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.38 ppm	ACGIH 2006a

## 2. HUMAN TOXICITY DATA

### 2.1. Acute Lethality

#### 2.1.1. Case Reports

No case reports were located.

### 2.2. Nonlethal Toxicity

#### 2.2.1. Odor Threshold/Odor Awareness

The odor is described as pungent and irritating (NIOSH 2006). No information on the odor threshold was found.

#### 2.2.2. Case Reports

No case reports were located.

#### 2.2.3. Epidemiologic Studies

No epidemiologic studies were located.

### 2.3. Developmental/Reproductive Toxicity

No data regarding developmental/reproductive toxicity in humans were located.

### 2.4. Genotoxicity

No data regarding genotoxicity in humans were located.

## 2.5. Carcinogenicity

No data regarding carcinogenicity in humans were located.

## 2.6. Summary

No information on human exposure was available. Carbonyl fluoride is a strong irritant to the skin, eyes, mucous membranes, and respiratory tract; direct contact with the skin may cause frostbite (O'Neil et al. 2001).

## 3. ANIMAL TOXICITY DATA

### 3.1. Acute Lethality

#### 3.1.1. Rats

Studies were conducted by the DuPont Company (1959) in which groups of 2 rats (male Chr-CD) inhaled nominal concentrations of 5 or 10 ppm and 6 rats inhaled 100 ppm for 4 hr. Rats that died (3/6) showed acute tracheobronchitis and pulmonary congestion. Survivors, 3/6 rats in the 100 ppm group - exhibited no pathological changes. The 4-hr LC<sub>50</sub> was approximately 100 ppm. The data were presented in a table of a one page preliminary report.

Scheel et al. (1968a) evaluated the acute inhalation toxicity of carbonyl fluoride to groups of ten 8- and 24-week old Greenacres Controlled Flora male and female rats (5/sex). The carbonyl fluoride was generated by polytetrafluoroethylene pyrolysis at 550°C. The authors referenced work by Coleman et al. (1968) which identified carbonyl fluoride as a principal toxic component of the pyrolysis gases as their rationale for using polytetrafluoroethylene pyrolysis to produce carbonyl fluoride. Atmospheres were generated with a metered air stream into the exposure chamber, and concentrations were measured by the hydrolysable fluoride method. Rats were exposed to various concentrations with the lowest being 310 ppm for 1 hour, followed by a 14-day observation period. (With the exception of the 310 ppm value, actual concentrations were not provided). Deaths usually occurred within 24 hours with few latent deaths. The LC<sub>50</sub> values for the 8- and 24-week old rats were 360 and 460 ppm, respectively. Although an age difference in mortality was apparent, no difference in mortality between the sexes was apparent. Exposure to 310 ppm resulted in focal hemorrhage of the lung and pulmonary edema, observed at 24 hours postexposure. The authors stated that this effect was produced at the same concentration in other species including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lung were not provided for these species. At 48 hours postexposure, the lung showed rapid cellular reorganization and clearing of edema; but alveolar damage was still present. Extravasation of red cells from damaged capillaries continued for up to 7 days; this effect was accompanied by mild interstitial fibrosis. Although data were not provided, Scheel et al. (1968a) reported that a 4-hour exposure to 90 ppm also resulted in approximately 50% mortality.

DuPont (1976) exposed male Chr-CD rats (10/group) to > 97% pure carbonyl fluoride for 4 hr to 26.7, 30.8, 32.7, 41.3, 44.7, 47.2 (48.8 by IR), or 47.6 ppm. Test atmospheres were analyzed with a fluoride specific electrode and confirmed by infra-red analysis. Deaths occurred at every concentration. Mortalities in the respective groups were 5/10, 3/10, 3/10, 6/10, 8/10,

9/10, and 6/10. The calculated LC<sub>50</sub> was 34.3 ppm. The calculated BMC<sub>01</sub> was 10.4 ppm and the BMCL<sub>05</sub> was 5.2 ppm. Respiration in the rats varied directly with exposure concentration and ranged from rapid shallow to convulsive respiration. Pathological examination found white plaques, red focal spots, consolidation and edema of the lungs. There was also liver congestion, and the spleens were bright red.

### 3.2. Nonlethal Toxicity

#### 3.2.1. Rats

Male albino rats (4/group) were exposed to nominal concentrations of 2.5 or 5 ppm of carbonyl fluoride for 2 and 2.5 hr in a preliminary investigation of toxicity (DuPont, 1956). The rats were then observed for 24 hr or 8 days. The low concentration 2 ppm was not lethal to the rats and no clinical signs developed. At 5 ppm the rats developed slight dyspnea and cyanosis. No other information was reported.

Studies were conducted by the DuPont Company (1959) in which groups of 2 rats (male ChR-CD) inhaled nominal concentrations of 5 or 10 ppm and 6 rats inhaled 100 ppm for 4 hr. Clinical signs included rapid, shallow respiration with loss of weight in the 5 and 10 ppm groups. All rats in the 5 and 10 ppm group exhibited no pathological changes. The data were presented in a table of a one page preliminary report.

**TABLE 3. Summary of Acute Inhalation Data in Laboratory Animals**

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	2.5 <sup>a</sup>	2, 2.5 hr	none	DuPont 1956
	5.0 <sup>a</sup>	2, 2.5 hr	slight dyspnea and cyanosis	
Rat	5 <sup>a</sup>	4 hr	rapid, shallow respiration	DuPont 1959
	10 <sup>a</sup>	4 hr	rapid, shallow respiration	
	100 <sup>a</sup>	4 hr	LC <sub>50</sub> , pulmonary congestion	
Rat				Scheel et al. 1968a*
8-weeks old	360	1 hr	LC <sub>50</sub>	
24-weeks old	460	1 hr	LC <sub>50</sub>	
8-weeks old	90	4 hr	LC <sub>50</sub>	
Rat	26.7	4 hr	50 % mortality	DuPont 1976
	30.8		30% mortality	
	32.7		30% mortality	
	34.3		LC <sub>50</sub> (calculated)	
	41.3		60% mortality	
	44.7		80% mortality	
	47.2 (48.8 IR)		90% mortality	
	47.6		60% mortality	

<sup>a</sup> Nominal concentrations.

\*Exposed rats to polytetrafluoroethylene pyrolysis products (550°C) and reported concentrations of measured fluoride.

### 3.3. Repeated Dose Toxicity

Scheel et al. (1968b) examined whether the toxic action of carbonyl fluoride is based on the toxic action of hydrogen fluoride. Twenty male and 20 female rats (Greenacres Controlled Flora) were tested with five, 1-hour, daily inhalation exposures of polytetrafluoroethylene pyrolysis products, temperature not reported. Although the authors state that the five one-hour exposures were to 50 ppm carbonyl fluoride, their total stated exposure of 158 ppm•hours as well as graphic data indicate that successive daily exposures were to 52, 43, 29, 25, and 9 ppm. Urine was collected and analyzed for fluoride, tissues were collected and analyzed for inhibition of succinic dehydrogenase, and urine was analyzed for protein, glucose, ketones, and occult blood. After five days of exposure (158 ppm-hours plus 18 grams of particulates) the mortality was 22%; rats died during or shortly after exposure, and rats that died exhibited extreme malaise and weakness. No deaths occurred until the 3<sup>rd</sup> day. Urinary fluoride increased from 3 to 42 mg/L in 5 days. Eighteen days after the last exposure, the urinary fluoride of exposed rats was four times that of the controls. Protein, glucose, ketones, and occult blood were detected in the urine. A 30% weight loss occurred subsequent to exposure. The succinic dehydrogenase activity in the kidney was inhibited to less than 5% of its normal value. Increased levels of succinic dehydrogenase activity were produced in the lung. The liver showed enlarged nuclei and fatty infiltration. The metabolic inhibition was reversible, as were the pathologic changes in the lungs (with the exception of a small amount of emphysematous change), liver and kidneys (examined at 18 days following exposure). The authors concluded that the toxic syndrome of carbonyl fluoride inhalation present in the pyrolysis products of polytetrafluoroethylene is compatible with the descriptions of hydrogen fluoride toxicity.

**TABLE 4. Repeated Dose Inhalation Data in Laboratory Animals**

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	9-52	1 hr/d for 5 d	22% mortality, reversible pathologic changes in lungs and liver	Scheel 1968b

### 3.4. Developmental/Reproductive Toxicity

No data on developmental/reproductive toxicity were located.

### 3.5. Genotoxicity

No data on genotoxicity were located.

### 3.6. Chronic Toxicity/Carcinogenicity

No data on chronic toxicity/carcinogenicity were located.

### 3.7. Summary

Acute inhalation of carbonyl fluoride in rats causes rapid or labored respiration and respiratory irritation, pulmonary congestion and edema, increases urinary fluoride excretion, proteinuria, and can cause death. The acute inhalation data on rats had varying LC<sub>50</sub> values. The LC<sub>50</sub>'s of the studies were 100 ppm at 4 hr, 360 ppm at 1 hr (8 week old rat), 460 ppm at 1 hr (24

week old rat), 90 ppm at 4 hr, and 34.3 at 4 hr (DuPont, 1959; Scheel et al. 1968a; DuPont, 1976). The rat 1 hr LC<sub>50</sub> for hydrogen fluoride (HF) is 1278 ppm (MacEwen and Vernot, 1970). Converting the 460 ppm carbonyl fluoride to HF gives 867 ppm which suggests that carbonyl fluoride produces toxicity beyond that caused by HF released by hydrolysis. Converting the HF LC<sub>50</sub> to equivalent carbonyl fluoride gives a predicted value for carbonyl fluoride of 680 ppm, nearly 50% greater than that observed. No data were located on developmental/reproductive toxicity, genotoxicity, or chronic toxicity/carcinogenicity.

#### 4. SPECIAL CONSIDERATIONS

##### 4.1. Metabolism and Disposition

Carbonyl fluoride is hygroscopic and hydrolyzed in the moist respiratory tract to carbon dioxide and two moles of hydrogen fluoride (Arito and Soda 1977). Hydrogen fluoride is soluble in water and absorbed by the respiratory tract (HSDB 2006). It has a relatively low dissociation constant ( $3.5 \times 10^{-4}$ ) which allows the non-ionized compound to penetrate the skin, respiratory system, or gastrointestinal tract. The fluoride ion is readily absorbed into the bloodstream and is carried to all organs. Equilibrium is rapidly reached (Perry et al. 1994). Elimination is primarily through the kidneys.

##### 4.2. Mechanism of Toxicity

Carbonyl fluoride is a contact irritant that hydrolyzes in the presence of water to hydrogen fluoride. Hydrogen fluoride is irritating to the skin, eyes, and respiratory tract. Exposure via inhalation produces pulmonary hemorrhage, congestion, and death in laboratory animals (HSDB, 2005). Carbon dioxide is also produced when carbonyl fluoride is hydrolyzed. However, carbon dioxide toxicity occurs at very high concentrations, and the 10-hr time weighted average is currently set at 5000 ppm (NIOSH 2005).

##### 4.3. Structure Activity Relationships

Carbonyl fluoride is the fluorine analogue of phosgene (carbonyl chloride). However, in contact with moisture, only a small amount of phosgene hydrolyzes (NRC 2002), whereas, carbonyl fluoride is “instantly hydrolyzed by water” (O’Neil et al. 2001). The primary mechanism of action of phosgene is acylation resulting in lipid and protein denaturation, irreversible membrane changes, and disruption of enzymatic function. Death is caused by pulmonary edema following a latency period of greater than or equal to 24 hours (NRC 2002). The mechanism of action is unknown for carbonyl fluoride. A latency period was not reported by DuPont (1976), but Scheel et al. (1968a) reported that deaths usually occurred within 24 hours of exposure with few latent deaths. In the DuPont (1976) study, a 4-hr exposure to carbonyl fluoride in rats led to pulmonary consolidation and edema. Scheel et al. (1968a) reported deep lung focal hemorrhage and edema in rats exposed for 1 hr to carbonyl fluoride produced from polytetrafluoroethylene pyrolysis.

##### 4.4. Other Relevant Information

No additional relevant information was located.

#### 4.4.1. Species Variability

According to Scheel et al. (1968a), pathologic changes in the respiratory tract and liver following exposure to 310 ppm carbonyl fluoride for one hour were similar in the dog, rat, mouse, rabbit, and guinea pig.

#### 4.4.2. Susceptible Populations

No information was available on populations especially sensitive to carbonyl fluoride toxicity. However, the steep concentration-response curve implies limited intraspecies variability. Rats exposed to 2.5 ppm for 2 or 2.5 hours exhibited no clinical signs of toxicity (DuPont 1956). Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976).

#### 4.4.3. Concentration-Exposure Duration Relationship

The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by  $C^n \times t = k$ , where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent  $n$ , temporal scaling was performed, using  $n = 3$  when extrapolating to shorter time points and  $n = 1$  when extrapolating to longer time points using the  $C^n \times t = k$  equation (NRC 2001).

#### 4.4.4. Concurrent Exposure Issues

No concurrent exposure issues were identified.

### 5. DATA ANALYSIS FOR AEGL-1

#### 5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were identified.

#### 5.2. Summary of Animal Data Relevant to AEGL-1

Male albino rats were exposed to nominal concentrations of 2.5 or 5 ppm of carbonyl fluoride for 2 and 2.5 hr (DuPont 1956). The low concentration 2 ppm was not lethal to the rats and no clinical signs developed.

#### 5.3. Derivation of AEGL-1- Values

Although animal data were available, insufficient study details were available to consider use of DuPont (1956) for AEGL-1 derivation.

**TABLE 5. AEGL-1 Values for Carbonyl Fluoride**

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

NR = Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2

concentration is without adverse effects.

## 6. DATA ANALYSIS FOR AEGL-2

### 6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values were identified.

### 6.2. Summary of Animal Data Relevant to AEGL-2

No animal data relevant to development of AEGL-2 values were identified.

### 6.3. Derivation of AEGL-2 Values

Experimental data were not available to empirically derive an AEGL-2 value. Rats exposed to nominal concentrations of 5 or 10 ppm of carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976). In the absence of empirical data, and in accord with AEGL derivation guidelines for chemicals with steep dose-response curves, the AEGL-2 values for carbonyl fluoride were set at one-third of the AEGL-3 values (NRC 2001).

**TABLE 6. AEGL-2 Values for Carbonyl Fluoride**

10-minute	30-minute	1-hour	4-hour	8-hour
0.35 ppm (0.95 mg/m <sup>3</sup> )	0.35 ppm (0.95 mg/m <sup>3</sup> )	0.28 ppm (0.76 mg/m <sup>3</sup> )	0.17 ppm (0.46 mg/m <sup>3</sup> )	0.087 ppm (0.23 mg/m <sup>3</sup> )

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were identified.

### 7.2. Summary of Animal Data Relevant to AEGL-3

DuPont (1976) exposed male Chr-CD rats to carbonyl fluoride for 4 hr to 26.7, 30.8, 32.7, 41.3, 44.7, 47.2, or 47.6 ppm. Deaths occurred at every concentration. The calculated LC<sub>50</sub> was 34.3 ppm. The calculated BMC<sub>01</sub> was 10.4 ppm and the BMCL<sub>05</sub> was 5.2 ppm (DuPont 1976). Scheel et al. (1968) data was not considered relevant because animals were not exposed to pure carbonyl fluoride gas, but the pyrolysis products of polytetrafluoroethylene which include carbonyl fluoride (Arito and Soda, 1977).

### 7.3. Derivation of AEGL-3 Values

The AEGL-3 values were derived by applying the BMCL<sub>05</sub> of 5.2 ppm from DuPont (1976). The BMCL<sub>05</sub> was more conservative than the BMC<sub>01</sub> calculated from the DuPont (1976) study. Rapid to convulsive respiration and pulmonary edema were observed in rats exposed for 4 hours. Death occurred at all concentrations. An interspecies uncertainty factor of 3 was applied because it is not expected that the toxicity of the direct acting irritant would differ among species. Some

support is provided by Scheel et al. (1968a) who generated carbonyl fluoride via polytetrafluoroethylene pyrolysis. Exposure to 310 ppm in rats resulted in focal hemorrhage of the lung and pulmonary edema, observed at 24 hours postexposure. The authors stated that this effect was produced at the same concentration in other species including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lung were not provided for these species. Carbonyl fluoride also has a steep concentration-response curve. Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976). An intraspecies uncertainty factor of 3 was applied because carbonyl fluoride is a direct acting irritant of the lung and the respiratory effects due to irritation are not expected to differ greatly among individuals. Carbonyl fluoride also has a steep-concentration response which may be an indication of a small variation of toxic effects within a population.

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases has been described by the relationship  $c^n \times t = k$ , where the exponent  $n$  ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically derived exponent, temporal scaling was performed using  $n = 3$ , when extrapolating to shorter time points and  $n = 1$  when extrapolating to longer time points for AEGL values (NRC 2001).

**TABLE 7. AEGL-3 Values for Carbonyl Fluoride**

10-minute	30-minute	1-hour	4-hour	8-hour
1.0 ppm (2.7 mg/m <sup>3</sup> )	1.0 ppm (2.7 mg/m <sup>3</sup> )	0.83 ppm (2.2 mg/m <sup>3</sup> )	0.52 ppm (1.4 mg/m <sup>3</sup> )	0.26 ppm (0.70 mg/m <sup>3</sup> )

## 8. SUMMARY OF AEGLS

### 8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values are not recommended due to insufficient data. AEGL-2 values are based on a three fold reduction of the AEGL-3 values because experimental data were not available to empirically derive a AEGL-2 value. AEGL-3 values are based on the benchmark dose response calculation of the 5% response for lethality. AEGL values for carbonyl fluoride are listed in Table 8.

**TABLE 8. Summary of AEGL Values for Carbonyl Fluoride**

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.35 ppm (0.95 mg/m <sup>3</sup> )	0.35 ppm (0.95 mg/m <sup>3</sup> )	0.28 ppm (0.76 mg/m <sup>3</sup> )	0.17 ppm (0.46 mg/m <sup>3</sup> )	0.087 ppm (0.23 mg/m <sup>3</sup> )
AEGL-3 (Lethal)	1.0 ppm (2.7 mg/m <sup>3</sup> )	1.0 ppm (2.7 mg/m <sup>3</sup> )	0.83 ppm (2.2 mg/m <sup>3</sup> )	0.52 ppm (1.4 mg/m <sup>3</sup> )	0.26 ppm (0.70 mg/m <sup>3</sup> )

NR = not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

### 8.2. Comparison with Other Standards and Guidelines

Extant standards and guidelines for carbonyl fluoride are listed in Table 9. No other emergency standards such as Emergency Response Planning Guidelines (ERPGs) or a NIOSH Immediately Dangerous to Life and Health (IDLH) are available for carbonyl fluoride. The American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average is based on data from Scheel et al. (1968a). The 8-hour AEGL values are much lower than the industrial standards and guidelines for carbonyl fluoride.

**TABLE 9. Extant Standards and Guidelines for Carbonyl Fluoride**

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.35 ppm	0.35 ppm	0.28 ppm	0.17 ppm	0.087 ppm
AEGL-3	1.0 ppm	1.0 ppm	0.83 ppm	0.52 ppm	0.26 ppm
REL-TWA (NIOSH) <sup>a</sup>					2 ppm
REL-STEEL (NIOSH) <sup>b</sup>					5 ppm
TLV-TWA (ACGIH) <sup>c</sup>					2 ppm
TLV-STEEL (ACGIH) <sup>d</sup>					5 ppm
MAC Peak Limit (The Netherlands) <sup>e</sup>					0.5 ppm

NR = not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

<sup>a</sup>NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2006) is defined as the time-weighted average concentration for up to a 10-hour workday during a 40-hr workweek.

<sup>b</sup>NIOSH REL-STEEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH 2006) is defined as a 15-minute time weighted average exposure that should not be exceeded at any time during the workday.

<sup>c</sup>ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2006) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

<sup>d</sup>ACGIH TLV-STEEL (Threshold Limit Value - Short Term Exposure Limit) (ACGIH 2006) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

<sup>e</sup>MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]) Nationale MAC List (2000). (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000 is defined analogous to the ACGIH-TLV-TWA.

### 8.3. Data Adequacy and Research Needs

There are no human data available regarding exposure to carbonyl fluoride. DuPont (1956, 1959, and 1976) exposed rats from two to four hours, but the two earlier studies had nominal concentrations, used relatively few animals, and reported very few study details. Scheel et al.

1 (1968a, 1968b) exposed rats to carbonyl fluoride produced by burning polytetrafluoroethylene.  
2 While carbonyl fluoride is a major pyrolysis product, it is not the only pyrolysis product  
3 produced (Arito and Soda 1977) and the rats were probably exposed to other compounds that  
4 contain fluoride. The animals were also exposed to the particulate matter produced from  
5 polytetrafluoroethylene pyrolysis which may have increased effects observed. Additional acute  
6 animal studies in other species and with a greater range of concentrations would be helpful in  
7 deriving AEGL values.

## 9. REFERENCES

- ACGIH (American Conference of Government and Industrial Hygienists). 2006a. Documentation of the Threshold Limit Values and Biological Exposure Indices: Carbonyl fluoride. Sixth ed., ACGIH, Cincinnati, OH.
- ACGIH (American Conference of Government and Industrial Hygienists). 2006b. Documentation of the Threshold Limit Values and Biological Exposure Indices: Hydrogen fluoride. Sixth ed., ACGIH, Cincinnati, OH.
- Arito, H. and R. Soda. 1977. Pyrolysis products of polytetrafluoroethylene and polyfluoroethylenepropylene with reference to inhalation toxicity. *Ann. Occup. Hyg.* 20:247-255.
- Coleman, E., L.D. Scheel, R. Kupel, and R. Larkin. 1968. The identification of toxic compounds in the pyrolysis of polytetrafluoroethylene. *Am. Ind. Hyg. Assoc. J.* 29:33.
- DuPont (E.I. DuPont de Nemours and Company, Inc.). 1956. Toxicity Studies of Pyrolysis Products of Fluorinated Polymers (Teflon Polytetrafluoroethylene) with Cover Letter Dated 101292: Initial Submission. Haskell Laboratory Report No. 18-56. DuPont Co., Haskell Laboratory, Newark. DE.
- DuPont (E.I. DuPont de Nemours and Company, Inc.). 1959. Toxicity Studies of Carbonyl Fluoride. Haskell Laboratory Report No. 32-59. DuPont Co., Haskell Laboratory, Newark. DE.
- DuPont (E.I. DuPont de Nemours and Company, Inc.). 1976. Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont Co., Haskell Laboratory, Newark. DE.
- HSDB (Hazardous Substances Data Bank). 2005. Hydrofluoric Acid. Online data base, . National Library of Medicine <http://toxnet.nlm.nih.gov>.
- HSDB (Hazardous Substances Data Bank). 2006. Carbonyl Fluoride: Online data base, National Library of Medicine: <http://toxnet.nlm.nih.gov/cgi-bin/sis>.
- Lund, K., J. Ekstrand, J. Boe, P. Sostrand, and J. Kongerud. 1997. Exposure to hydrogen fluoride: An experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. *Occup. Environ. Med.* 54:32-37.
- Lund, K., M. Refsnes, T. Sandstrom, P. Sostrand, P. Schwarze, J. Boe, and J. Kongerud. 1999. Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. *Scand. J. Work Environ. Health* 25:326-334.
- MAC Ministry of Social Affairs and Employment (SDU Uitgevers). 2000. National MAC (Maximum Allowable Concentration) List. The Hague, The Netherlands.

- MacEwen, J.D., Vernot, E.H. 1970. Toxic Hazards Research Unit Annual Technical Report: 1970. AMRL-TR-70-77, AD 714694. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio.
- NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards- Carbon Dioxide. Online data base, U.S. Department of Health and Human Services: <http://www.cdc.gov/niosh/npg/npgd0103.html>.
- NIOSH (National Institute for Occupational Safety and Health). 2006. NIOSH Pocket Guide to Chemical Hazards- Carbonyl Fluoride. Online data base, U.S. Department of Health and Human Services: <http://www.cdc.gov/niosh/npg/npgd0108.html>.
- NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. The National Academies Press, Washington, DC.
- NRC (National Research Council). 2002. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 2: Phosgene. The National Academies Press, Washington, DC.
- NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 4: Hydrogen Fluoride, pp. 123-197. The National Academies Press, Washington, DC.
- O'Neil, M.J., A. Smith, and P.E. Heckelman (eds.). 2001. Carbonyl fluoride. The Merck Index, p. 306. Whitehouse Station, NJ: Merck & Co.
- Perry, W.G., F.A. Smith and M.B. Kent. 1994. Chapter Forty-three: The Halogens, In: Patty's Industrial Hygiene and Toxicology, Volume II, Part F, G.F. Clayton and F.E. Clayton (eds). John Wiley & Sons, Inc., New York.
- Scheel, L.D., W.C. Lane, and W.E. Coleman. 1968a. The toxicity of polytetrafluoroethylene pyrolysis products – including carbonyl fluoride and a reaction product, silicon tetrafluoride. Am. Ind. Hyg. Assoc. J. 29:41-48.
- Scheel L.D., L. McMillan, and F.C. Phipps. 1968b. Biochemical changes associated with toxic exposures to polytetrafluoroethylene pyrolysis products. Am. Ind. Hyg. Assoc. J. 29:49-53.
- ten Berge, W.F., Zwart, A., Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Materials: 13: 301-309.

1  
2

**APPENDIX A: Derivation of AEGL Values**

**Derivation of AEGL-1 Value for Carbonyl Fluoride**

Key Study: AEGL-1 values were not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Toxicity endpoint: None

Time scaling: None

Uncertainty factors: None

Modifying factor: None

Calculations: None

10-minute AEGL-1 NR

30-minute AEGL-1 NR

1-hour AEGL-1 NR

4-hour AEGL-1 NR

8-hour AEGL-1 NR

**Derivation of AEGL-2 Values for Carbonyl Fluoride**

In the absence of empirical data, and in accord with AEGL derivation guidelines for chemicals with steep dose-response curves, the AEGL-2 values for carbonyl fluoride were set at one-third of the AEGL-3 values (NRC 2001). Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976).

**Calculations**

10-minute AEGL-2:	$1.04 \text{ ppm}/3 = 0.35 \text{ ppm}$
30-minute AEGL-2:	$1.04 \text{ ppm}/3 = 0.35 \text{ ppm}$
1-hour AEGL-2:	$0.83 \text{ ppm}/3 = 0.28 \text{ ppm}$
4-hour AEGL-2:	$0.52 \text{ ppm}/3 = 0.17 \text{ ppm}$
8-hour AEGL-2:	$0.26 \text{ ppm}/3 = 0.087 \text{ ppm}$

**Derivation of AEGL-3 Values for Carbonyl Fluoride**

Key Study: DuPont (E.I. DuPont de Nemours and Company, Inc.). 1976. Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont Co., Haskell Laboratory, Newark. DE

Toxicity endpoint: Threshold for lethality; BMCL<sub>05</sub> (5.2 ppm)

Uncertainty factors: An interspecies uncertainty factor of 3 was applied because it is not expected that the toxicity of the direct acting irritant would differ among species. Some support is provided by Scheel et al. (1968a) who generated carbonyl fluoride via polytetrafluoroethylene pyrolysis. Exposure to 310 ppm in rats resulted in focal hemorrhage of the lung and pulmonary edema, observed at 24 hours postexposure. The authors stated that this effect was produced at the same concentration in other species including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lung were not provided for these species. Carbonyl fluoride also has a steep concentration-response curve. Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$  ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976). An intraspecies uncertainty factor of 3 was applied because carbonyl fluoride is a direct acting irritant of the lung and the respiratory effects due to irritation are not expected to differ greatly among individuals. Carbonyl fluoride also has a steep-concentration response which may be an indication of a small variation of toxic effects within a population.

Modifying factor: None applied

Time scaling: The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases has been described by the relationship  $C^n \times t = k$ , where the exponent  $n$  ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically derived exponent, temporal scaling was performed using  $n = 3$ , when extrapolating to shorter time points and  $n = 1$  when extrapolating to longer time points for AEGL values (NRC 2001). The 30-minute AEGL-2 value was adopted for the 10-minute value according to the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001).

Calculations:  $5.2 \text{ ppm}/10 = 0.52 \text{ ppm}$

$$C^n \times t = k$$

$$(0.52 \text{ ppm})^3 \times 240 \text{ min} = 33.74592 \text{ ppm}^3 \cdot \text{min}$$

$$C \times t = k$$

$$0.52 \text{ ppm} \times 240 \text{ minutes} = 124.8 \text{ ppm} \cdot \text{min}$$

$$10\text{-minute AEGL-3: } C^3 \times 30 \text{ minutes} = 33.74592 \text{ ppm}^3 \cdot \text{min}$$

$$C = 1.0 \text{ ppm}$$

$$30\text{-minute AEGL-3: } C^3 \times 30 \text{ minutes} = 33.74592 \text{ ppm}^3 \cdot \text{min}$$

$$C = 1.0 \text{ ppm}$$

$$1\text{-hour AEGL-3: } C^3 \times 60 \text{ minutes} = 33.74592 \text{ ppm}^3 \cdot \text{min}$$

**CARBONYL FLUORIDE****INTERIM: 05/2008**

1		$C = 0.83 \text{ ppm}$
2	4-hour AEGL-3:	$C \times 240 \text{ minutes} = 124.8 \text{ ppm} \cdot \text{min}$
3		$C = 0.52 \text{ ppm}$
4	8-hour AEGL-3:	$C \times 480 \text{ minutes} = 124.8 \text{ ppm} \cdot \text{min}$
5		$C = 0.26 \text{ ppm}$

**APPENDIX B: Time-Scaling Calculations**

1  
2       The concentration exposure time relationship for many irritant and systemically acting  
3 vapors and gases may be described by  $C^n \times t = k$ , where the exponent ranges from 0.8 to 3.5 (ten  
4 Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent  
5 n, temporal scaling was performed, using  $n = 3$  when extrapolating to shorter time points and  $n =$   
6 1 when extrapolating to longer time points using the  $C^n \times t = k$  equation (NRC 2001).

# APPENDIX C: Derivation Summary for Carbonyl Fluoride AEGLs

## Acute Exposure Guideline Levels for Carbonyl Fluoride (CAS Reg. No. 353-50-4) Derivation Summary

### AEGL-1 VALUES

No AEGL-1 values were derived due to insufficient data.

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR
Key Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects:				
ppm				
ppm				
ppm				
ppm				
ppm				
ppm				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale:				
Total uncertainty factor:				
Interspecies:				
Intraspecies:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy:				

NR:= Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL concentration is without adverse effects.

## AEGL-2 VALUES

10-minute 0.35 ppm	30-minute 0.35 ppm	1-hour 0.28 ppm	4-hour 0.17 ppm	8-hour 0.087 ppm
Key Reference: DuPont (E.I. DuPont de Nemours and Company, Inc.). 1976. Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont Co., Haskell Laboratory, Newark, DE				
Test Species/Strain/Number: Rat/Chr-CD/10 per group				
Exposure Route/Concentrations/Durations: Inhalation/26.7, 30.8, 32.7, 41.3, 44.7, 47.2, 47.6/ 4 hour				
Effects: Rapid shallow respiration, pulmonary edema				
Endpoint/Concentration/Rationale: The AEGL-2 values were derived by dividing the AEGL-3 values by 3. This procedure, based on NRC (2001), is applicable for chemicals with steep dose-response curves. Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$ ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976).				
Uncertainty Factors/Rationale: See AEGL-3 derivation summary below.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applied				
Time Scaling: See AEGL-3 derivation.				
Data Adequacy: See AEGL-3 derivation				

## AEGL-3 VALUES

10-minute 1.0 ppm	30-minute 1.0 ppm	1-hour 0.83 ppm	4-hour 0.52 ppm	8-hour 0.26 ppm
Key Reference: DuPont (E.I. DuPont de Nemours and Company, Inc.). 1976. Acute Inhalation Toxicity Studies of Hydrogen Fluoride and Carbonyl Fluoride. Haskell Laboratory Report No. 485-76. DuPont Co., Haskell Laboratory, Newark. DE				
Test Species/Strain/Number: Rat/Chr-CD/10 per group				
Exposure Route/Concentrations/Durations: Inhalation/26.7, 30.8, 32.7, 41.3, 44.7, 47.2, 47.6/ 4 hour				
Effects: Rapid shallow respiration, pulmonary edema 26.7 ppm: 50% mortality 30.8 ppm: 30% mortality 32.7 ppm: 30% mortality 41.3 ppm: 60% mortality 44.7 ppm: 80% mortality 47.2 ppm: 90% mortality 47.6 ppm: 60% mortality				
Endpoint/Concentration/Rationale: The AEGL-3 was based on the threshold for lethality, BMCL <sub>05</sub> (5.2 ppm).				
Uncertainty Factors/Rationale: An interspecies uncertainty factor of 3 was applied because it is not expected that the toxicity of the direct acting irritant would differ among species. Some support is provided by Scheel et al. (1968a) who generated carbonyl fluoride via polytetrafluoroethylene pyrolysis. Exposure to 310 ppm in rats resulted in focal hemorrhage of the lung and pulmonary edema, observed at 24 hours postexposure. The authors stated that this effect was produced at the same concentration in other species including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lung were not provided for these species. Carbonyl fluoride also has a steep concentration-response curve. Rats exposed to 5 or 10 ppm carbonyl fluoride for 4 hr (DuPont 1956; 1959) experienced dyspnea and rapid shallow respiration. At higher concentrations ( $\geq 26.7$ ppm for 4 hr) death occurred indicating a steep exposure-response curve (DuPont, 1976). An intraspecies uncertainty factor of 3 was applied because carbonyl fluoride is a direct acting irritant of the lung and the respiratory effects due to irritation are not expected to differ greatly among individuals. Carbonyl fluoride also has a steep-concentration response which may be an indication of a small variation of toxic effects within a population.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applied				
Time Scaling: The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases has been described by the relationship $c^n \times t = k$ , where the exponent $n$ ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically derived exponent, temporal scaling was performed using $n = 3$ , when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points for AEGL values (NRC 2001).				
Data Adequacy: The study was well done with an appropriate number of animals. Analytical concentrations were measured and an endpoint consistent with the AEGL-3 definition was observed.				

1  
2

**APPENDIX D: Benchmark Dose Calculations**

BMDS MODEL RUN BMCL<sub>05</sub>

The form of the probability function is:

$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose}))$ ,

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3

Independent variable = COLUMN1

Slope parameter is restricted as slope  $\geq 1$

Total number of observations = 8

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to: 1e-008

Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

## Default Initial (and Specified) Parameter Values

background = 0

intercept = -7.52665

slope = 2.13336

## Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	intercept	slope
intercept	1	-1
slope	-1	1

## Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-6.88857	2.62927	-12.0418	-1.7353
slope	1.94933	0.724479	0.529374	3.36928

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

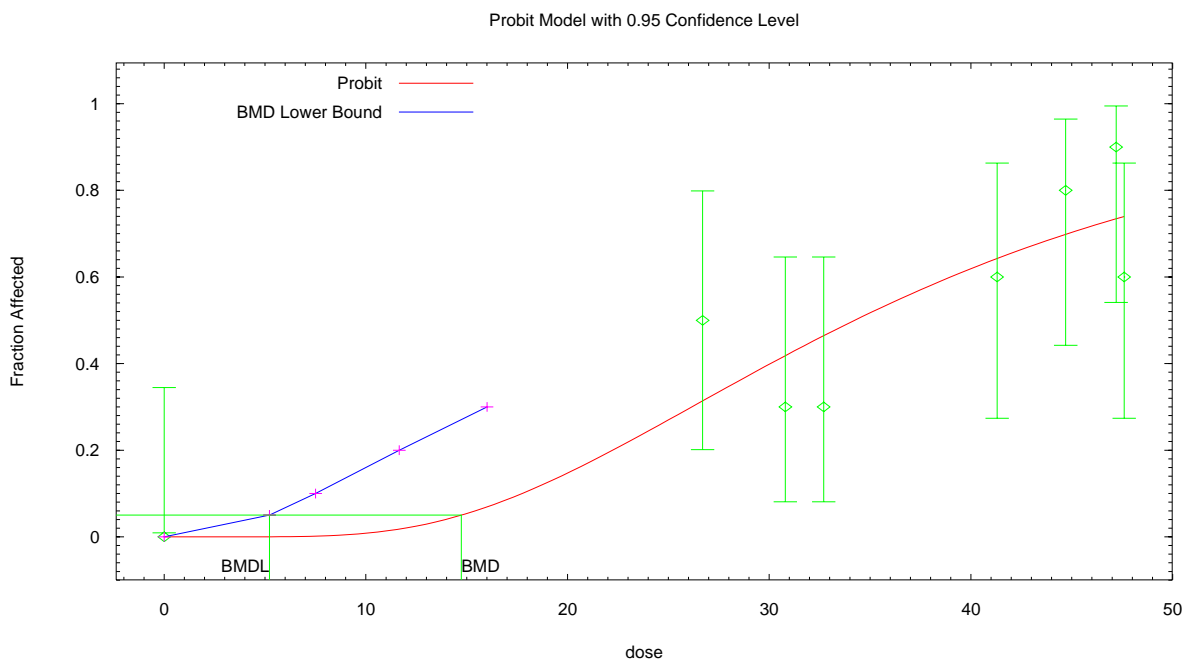
## Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.8638	8			
Fitted model	-44.0906	2	6.45349	6	0.3744
Reduced model	-55.4518	1	29.1759	7	0.0001344
AIC:	92.1812				

## Goodness of Fit

	Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
1						
2						
3						
4	0.0000	0.0000	0.000	0	10	0.000
5	26.7000	0.3136	3.136	5	10	1.271
6	30.8000	0.4179	4.179	3	10	-0.756
7	32.7000	0.4639	4.639	3	10	-1.039
8	41.3000	0.6423	6.423	6	10	-0.279
9	44.7000	0.6981	6.981	8	10	0.702
10	47.2000	0.7340	7.340	9	10	1.188
11	47.6000	0.7394	7.394	6	10	-1.004
12	Chi^2 = 6.26    d.f. = 6    P-value = 0.3951					

13  
 14 Benchmark Dose Computation  
 15 Specified effect = 0.05  
 16 Risk Type = Extra risk  
 17 Confidence level = 0.95  
 18 BMD = 14.7319  
 19 BMDL = 5.21965



07:45 01/08 2008

BMDS MODEL RUN BMC<sub>01</sub>

The form of the probability function is:

$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose}))$ , where  
 CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3

Independent variable = COLUMN1

Slope parameter is restricted as slope  $\geq 1$

1 Total number of observations = 8  
 2 Total number of records with missing values = 0  
 3 Maximum number of iterations = 250  
 4 Relative Function Convergence has been set to: 1e-008  
 5 Parameter Convergence has been set to: 1e-008  
 6 User has chosen the log transformed model  
 7

#### 8 Default Initial (and Specified) Parameter Values

9 background = 0  
 10 intercept = -7.52665  
 11 slope = 2.13336  
 12

#### 13 Asymptotic Correlation Matrix of Parameter Estimates

14 ( \*\*\* The model parameter(s) -background have been estimated at a boundary point, or have been  
 15 specified by the user, and do not appear in the correlation matrix )  
 16

	intercept	slope
intercept	1	-1
slope	-1	1

#### 21 Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-6.88857	2.62918	-12.0417	-1.73548
slope	1.94933	0.724454	0.529424	3.36923

28  
 29 NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus  
 30 has no standard error.  
 31

#### 32 Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.8638	8			
Fitted model	-44.0906	2	6.45349	6	0.3744
Reduced model	-55.4518	1	29.1759	7	0.0001344
AIC:	92.1812				

#### 41 Goodness of Fit

	Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
45	26.7000	0.3136	3.136	5	10	1.271
46	30.8000	0.4179	4.179	3	10	-0.756
47	32.7000	0.4639	4.639	3	10	-1.039
48	41.3000	0.6423	6.423	6	10	-0.279
49	44.7000	0.6981	6.981	8	10	0.702
50	47.2000	0.7340	7.340	9	10	1.188
51	47.6000	0.7394	7.394	6	10	-1.004

# CARBONYL FLUORIDE

INTERIM: 05/2008

0.0000 0.0000 0.000 0 10 0.000  
Chi<sup>2</sup> = 6.26 d.f. = 6 P-value = 0.3951

## Benchmark Dose Computation

Specified effect = 0.01

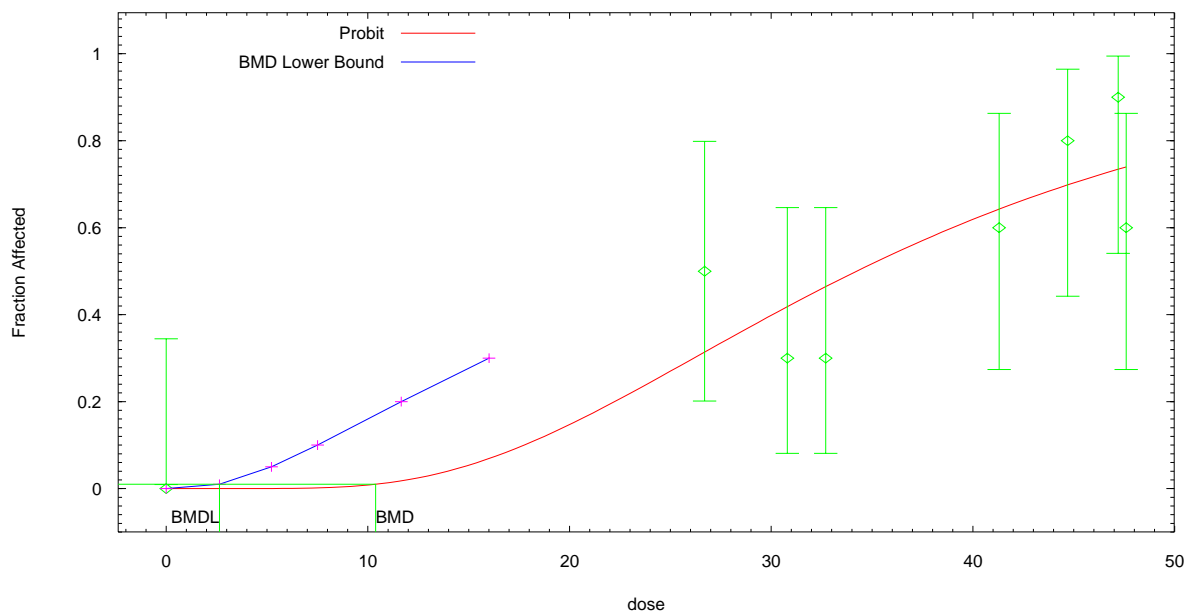
Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.3855

BMDL = 2.64042

Probit Model with 0.95 Confidence Level

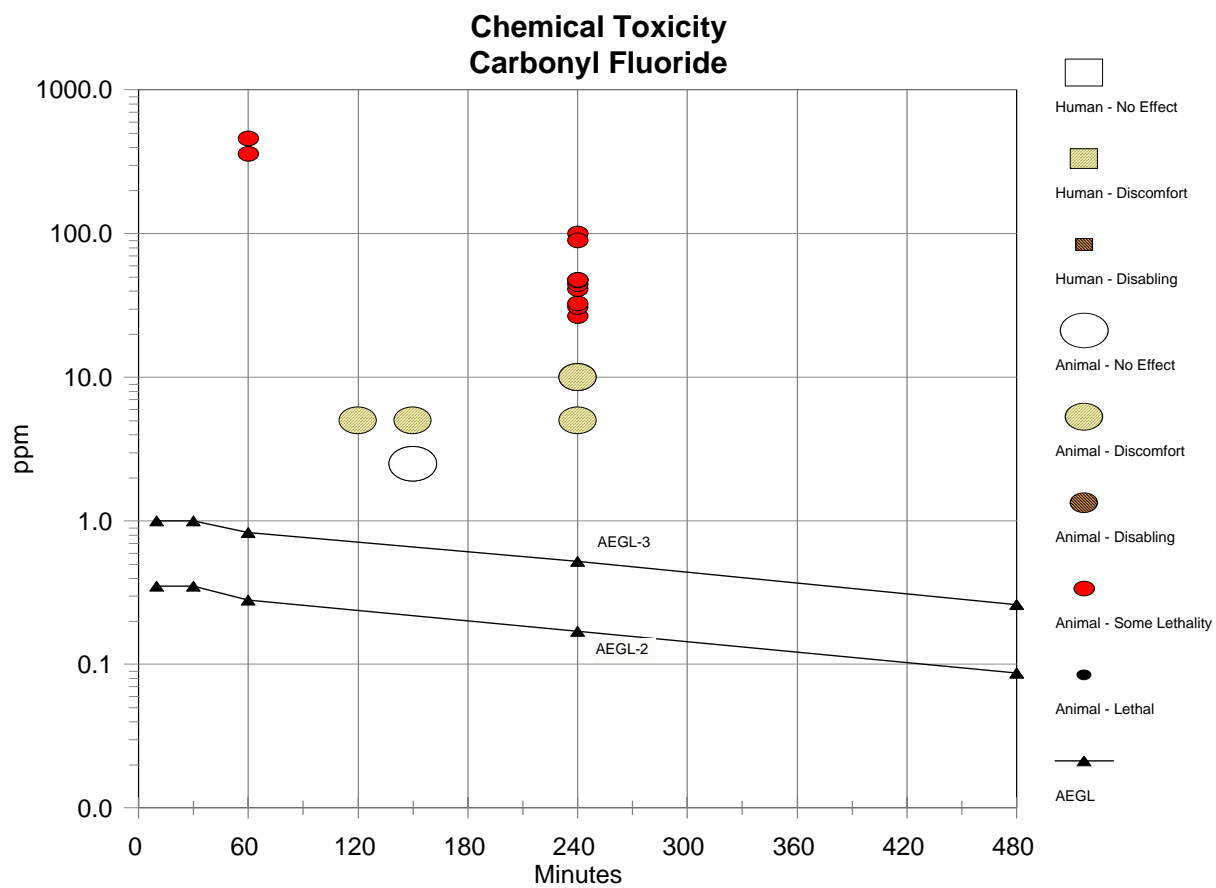


11:24 11/15 2007

1  
2  
3

**APPENDIX E: Category Plot for Carbonyl Fluoride**

1



2

**CARBONYL FLUORIDE**

**INTERIM: 05/2008**

1 Category Plot Data

							For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal
Source	Species	Sex	Exposures #	ppm	Time (min)	Category	Comments
NAC/AEGL-1					10	AEGL	
NAC/AEGL-1					30	AEGL	
NAC/AEGL-1					60	AEGL	
NAC/AEGL-1					240	AEGL	
NAC/AEGL-1					480	AEGL	
NAC/AEGL-2				0.35	10	AEGL	
NAC/AEGL-2				0.35	30	AEGL	
NAC/AEGL-2				0.28	60	AEGL	
NAC/AEGL-2				0.17	240	AEGL	
NAC/AEGL-2				0.087	480	AEGL	
NAC/AEGL-3				1	10	AEGL	
NAC/AEGL-3				1	30	AEGL	
NAC/AEGL-3				0.83	60	AEGL	
NAC/AEGL-3				0.52	240	AEGL	
NAC/AEGL-3				0.26	480	AEGL	
DuPont 1956	rat	M	1	2.5	120	0	No effect
DuPont 1956	rat	M	1	2.5	150	0	No effect
DuPont 1956	rat	M	1	5	120	1	Slight dyspnea; cyanosis
DuPont 1956	rat	M	1	5	150	1	Slight dyspnea; cyanosis
DuPont 1959	rat	M	1	5	240	1	Rapid, shallow respiration
DuPont 1959	rat	M	1	10	240	1	Rapid, shallow respiration
DuPont 1959	rat	M	1	100	240	SL	Pulmonary congestion
Scheel et al. 1968a	rat	B	1	360	60	SL	50% mortality
Scheel et al. 1968a	rat	B	1	460	60	SL	50% mortality
Scheel et al. 1968a	rat	B	1	90	240	SL	50% mortality
DuPont 1976	rat	M	1	26.7	240	SL	50% mortality
DuPont 1976	rat	M	1	30.8	240	SL	30% mortality
DuPont 1976	rat	M	1	32.7	240	SL	30% mortality
DuPont 1976	rat	M	1	41.3	240	SL	60% mortality
DuPont 1976	rat	M	1	44.7	240	SL	80% mortality
DuPont 1976	rat	M	1	47.2	240	SL	90% mortality
DuPont 1976	rat	M	1	47.6	240	SL	60% mortality

2